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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/374,721	08/13/99	KENTEN J	IGN-2004

HM22/0117

KEVIN M FARRELL PC
P O BOX 999
YORK HARBOR ME 03911

EXAMINER	
ZEMAN,R	
ART UNIT	**PAPER NUMBER**
1645	4

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Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/374,721	Applicant(s) Kenten et al.
	Examiner Robert A. Zeman	Group Art Unit 1645

☒ Responsive to communication(s) filed on *Oct 23, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-116* is/are pending in the application.

Of the above, claim(s) *1-81 and 101-116* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *82-100* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-116* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

Applicant's election of Group VI (claims 82-96) in Paper No. 13 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Additionally, due to the amendments to claims 97-100, they now fall in Group VI. Claims 1-81 and 101-116 are withdrawn from consideration as drawn to non-elected inventions. Claims 82-100 are pending and currently under examination.

Double Patenting

Claims 82-84, 88-91 and 96-100 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 76-79, 84-85, 87-90 and 93 of copending Application No. 09/026,276. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are drawn to methods of stimulating an immune response using ubiquitin fusion proteins.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 82-89 and 95-100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for **stimulating antibody production** in animals utilizing ubiquitin fused to gonadotropin releasing hormone (GnRH) or growth hormone , does not reasonably provide enablement for methods for stimulating **all immune responses** utilizing ubiquitin fused to **all self antigens**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The aforementioned claims broadly encompass an infinite array of ubiquitin fusion proteins which contain an equally limitless number of self epitopes. The specification discloses the fusion of GnRH to ubiquitin for the stimulation of a strong anti-GnRH response in order to suppress gamete maturation in both male and female pigs (see Examples 3-6 and 8-10) and the fusion of growth hormone in order to induce weight gain in pigs (see Example 7). The specification is non-enabling for the unlimited number of ubiquitin/self antigen fusion proteins which are encompassed by the scope of the claims. No material limitations for the ubiquitin fusion proteins have been recited in the claims. The claims encompass every conceivable structure (means) for achieving the stated property (result). The disclosed

ubiquitin/GnRH and ubiquitin/growth hormone fusion proteins have specific characteristics and properties and hence, may differ structurally, chemically, physically, and functionally from other ubiquitin/self antigen fusion proteins. Said claims are all drawn to inducing an "immune response" to a self antigen in an animal and hence, would be considered "autoimmune responses" by definition. Autoimmune responses are quite complex and not fully understood by those skilled in the art. Additionally, many autoimmune responses are deleterious to the health and well being of an animal (see Paul Fundamental Immunology, 3rd Edition. pp 1033-1083). Consequently, it would be impossible to predict what effect an immune response to a given self antigen would have on an animal. By application of the factors set forth in Ex parte Forman (230 USPQ546(Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed.Cir. 1988)), which include (1) quantity of experimentation, (2) guidance presented, (3) the predictability of the art, and (4) the breadth of the claims, in the instant application, the quantity of experimentation to determine which self-epitopes to be fused to the ubiquitin to achieve the desired immune response which are encompassed by the scope of the claims is practically infinite and the guidance provided by the specification is minimal. Coupled with the high degree of unpredictability of the art it would require undue experimentation to determine how to use all the possible ubiquitin/self antigen fusion proteins encompassed by the scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 87 and 91-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 87 recites the limitation "ubiquitin moiety" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 91-92 are rendered vague and indefinite by the use of the phrase "physiological consequences of administration to the animal". It is unclear what is being "administered" to the animal. Is Applicant referring to the fusion protein or some other entity? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 91-92 are rendered vague and indefinite by the use of the phrase "substantially similar". It is unclear what constitutes "similarity". What percentage of the effects of surgical castration must be present in order to be considered "substantially similar". At what point to they become dissimilar? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 82, 84, 88-89 and 97-100 are rejected under 35 U.S.C. 102(b) as being anticipated by Vannier et al. (Biochemistry, Vol. 35 pages 1358-1366, 1996-- IDS-6).

Vannier et al. disclose the expression of the extracellular domain of human follicle stimulating hormone receptor (hFSHR) in *E. coli* as a ubiquitin fusion protein (see abstract). Vannier et al. also disclose that immunization of mice with said fusion protein (Ub-hFSHR) resulted in high affinity anti-receptor monoclonal antibodies. Immunization of monkeys with said fusion protein also induced the formation of anti-receptor antibodies (see page 13359 second paragraph, and page 1365, last paragraph). Consequently, the disclosure of Vannier et al. anticipates all the limitations of the instant claims.

Claims 82, 84 and 97-99 are rejected under 35 U.S.C. 102(b) as being anticipated by Mouritsen et al. (WO 95/05849).

Mouritsen et al. disclose the attachment of one or more T cell epitopes into the highly conserved self protein ubiquitin (see pages 6-7). Mouritsen discloses 2 different ubiquitin fusion proteins: one containing the T-cell epitope ovalbumin (OVA 325-336) and the other containing the T-cell epitope HEL (50-61). Injection of said fusion proteins into mice elicited a strong antibody response to the fusion protein. Consequently , the disclosure of Mouritsen et al. anticipates all the limitations of the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 82-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vannier et al. (Biochemistry, Vol. 35 pages 1358-1366, 1996--- IDS-6) in view of van der Zee et al. (Vaccine Vol 13, No. 8, pages 753-758, 1995).

Vannier et al. disclose the expression of the extracellular domain of human follicle stimulating hormone receptor (hFSHR) in *E. coli* as a ubiquitin fusion protein (see abstract). Vannier et al. also disclose that immunization of mice with said fusion protein (Ub-hFSHR) resulted in high affinity anti-receptor monoclonal antibodies. Immunization of monkeys with said fusion protein also induced the formation of anti-receptor antibodies (see page 13359 second

paragraph, and page 1365, last paragraph). Vannier et al. differs from the claimed invention in that it doesn't disclose the use of gonadotropin releasing hormone (GnRH) as the self antigen (epitope). van der Zee et al. teach a fusion protein comprising GnRH fused to fimbriae for the development of a contraceptive vaccine for use in domestic animals (see abstract and Figure 4 on page 757). van der Zee et al. also disclose that GnRH is one of the most attractive vaccine components for the immunoneutralization because it is regarded as the key regulatory peptide in the reproduction cycle of mammals (see page 753, column 1). Finally, van der Zee et al. disclose that vaccination of female rats and bull calves with said fusion protein induced not only serological, but also pharmacological effects (see page 757) and as a consequence, that GnRH is a promising candidate for the use in the development of a contraceptive vaccine. Consequently it would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify ubiquitin fusion proteins disclosed by Vannier et al. to use GnRH as the self epitope as disclosed by van der Zee et al. since GnRH is considered the pivotal regulatory peptide in mammalian reproduction. and there is a demand for an effective, low cost means of controlling fertility in domestic animals. The resulting fusion protein would benefit from the increased stabilization , increased efficiency of translation and increased preservation of biological activity due to proper folding associated with ubiquitin fusion proteins, as well as the increased efficacy of associated with the use of the GnRH self antigen.

With respect to the claims directed to ubiquitin fusion proteins comprising non-contiguous eptitope containing segments , it would be obvious to attach more than one of the epitope in a

noncontiguous fusion to ubiquitin since such an attachment would be expected to increase the chance of the epitope being recognized by immune surveillance, and hence enhancing the stimulation of an immune response to said epitope.

With respect to the claims directed to the use of pigs as the animal being treated it would have been obvious to one of ordinary skill in the art at the time of the instant invention to treat pigs since GnRH is a major component in the reproductive cycle of all mammals.

With respect to claims directed to modifying the ubiquitin moiety to avoid cleavage, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to make such a modification to avoid said cleavage since expressing expression of the proteins as ubiquitin fusion proteins results in stable, properly folded biologically active proteins.

Claims 82-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mouritsen et al. (WO 95/05849) in view of van der Zee et al. (Vaccine Vol 13, No. 8, pages 753-758, 1995).

Mouritsen et al. disclose the attachment of one or more T cell epitopes into the highly conserved self protein ubiquitin (see pages 6-7). Mouritsen discloses 2 different ubiquitin fusion proteins: one containing the T-cell epitope ovalbumin (OVA 325-336) and the other containing the T-cell epitope HEL (50-61). Injection of said fusion proteins into mice elicited a strong antibody response to the fusion protein. Mouritsen et al. differs from the claimed invention in that it doesn't disclose the use of gonadotropin releasing hormone (GnRH) as the self antigen (epitope). van der Zee et al. teach a fusion protein comprising GnRH fused to fimbriae for the development of a contraceptive vaccine for use in domestic animals (see abstract and Figure 4 on

page 757). van der Zee et al. also disclose that GnRH is one of the most attractive vaccine components for the immunoneutralization because it is regarded as the key regulatory peptide in the reproduction cycle of mammals (see page 753, column 1). Finally, van der Zee et al. disclose that vaccination of female rats and bull calves with said fusion protein induced not only serological, but also pharmacological effects (see page 757) and as a consequence, that GnRH is a promising candidate for the use in the development of a contraceptive vaccine. Consequently it would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify ubiquitin fusion proteins disclosed by Mouritsen et al. to use GnRH as the self epitope as disclosed by van der Zee et al. since GnRH is considered the pivotal regulatory peptide in mammalian reproduction. and there is a demand for an effective, low cost means of controlling fertility in domestic animals. The resulting fusion protein would benefit from the increased stabilization , increased efficiency of translation and increased preservation of biological activity due to proper folding associated with ubiquitin fusion proteins, as well as the increased efficacy of associated with the use of the GnRH self antigen.

With respect to the claims directed to ubiquitin fusion proteins comprising non-contiguous eptitope containing segments , it would be obvious to attach more than one of the epitope in a noncontiguous fusion to ubiquitin since such an attachment would be expected to increase the chance of the epitope being recognized by immune surveillance, and hence enhancing the stimulation of an immune response to said epitope.

With respect to the claims directed to the use of pigs as the animal being treated it would have been obvious to one of ordinary skill in the art at the time of the instant invention to treat pigs since GnRH is a major component in the reproductive cycle of all mammals.

With respect to claims directed to modifying the ubiquitin moiety to avoid cleavage, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to make such a modification to avoid said cleavage since expressing expression of the proteins as ubiquitin fusion proteins results in stable, properly folded biologically active proteins.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can be reached between the hours of 7:30 am and 4:00 pm Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, Donna Wortman, Primary Examiner can be reached at (703) 308-1032 or the examiner's supervisor, Lynette Smith, can be reached at (703)308-3909.

DONNA WORTMAN
PRIMARY EXAMINER

Robert A. Zeman

January 16, 2001